

FOLDING IN LATTICE MODELS WITH SIDE CHAINS

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Abstract

The folding kinetics of three-dimensional lattice Go models with side chains is studied using two different Monte Carlo move sets. A flexible move set based on single, double and triple backbone moves is found to be far superior compared to the standard Monte Carlo dynamics. In accord with previous theoretical predictions we find that the folding time grows as a power law with the chain length and the corresponding exponent $\lambda \approx 3.7$ for Go models. The study shows that the incorporation of side chains dramatically slows down folding rates.

Key words: Protein folding, lattice model, side chain, Monte Carlo

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In recent years, considerable insight into the thermodynamics and kinetics of protein folding has been gained due to simple lattice and off-lattice models [1,2] with a small number of beads. In these toy models of proteins, the beads represent amino acids. The length of single domain proteins N ranges approximately from 30 to 200.

The dependence of folding times, t_f , on N is an interesting problem in protein physics. Based on analogy to polymer physics Thirumalai [3] predicted that the folding times, t_f , should grow with the chain length, N , by power laws, i.e

$$t_f \sim N^\lambda \quad (1)$$

if folding proceeds through direct pathways with a nucleation mechanism. This prediction has been supported by later studies [4,5]. For simple two-state folders λ was estimated to be between 3.8 and 4.2 [3]. Numerical studies using various lattice

models *without side chains* (SC) [4,5] indicated the dependence of λ on specifics of the model, dimensionality and temperature, T . For the optimal temperature T_{min} ($\approx T_F$, the folding temperature), at which folding is fastest, $\lambda \approx 6$ and ≈ 4 for random and designed sequences, respectively [4]. For the Go model [6] $\lambda \approx 3$ [4,5]. In these studies t_f is defined as a median value of the first passage times.

It is well known that lattice models in which only α -carbons are represented by single beads, are oversimplified models of real proteins. A next natural step to mimic more realistic features of proteins such as a dense core packing [7] is to include the rotamer degrees of freedom. One of the simplest models is a cubic lattice of a backbone (BB) sequence of N beads, to which a side bead representing a SC is attached [7]. The system has in total $2N$ beads. Fig. 1 shows a typical native conformation with a SC for $N = 18$. The kinetics and

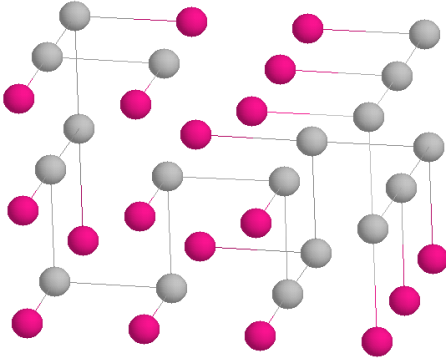


Fig. 1. Native conformation of lattice sequence with SC ($N = 18$). The BB and SC beads are denoted by grey and black circles, respectively.

thermodynamics of sequences with SCs were studied by Klimov and Thirumalai [7]. The SCs were shown [7] to enhance the cooperativity of folding.

The aim of this paper is twofold. First, we try to compare the efficiency of the standard move set (SMS) [8] and the one involving moves of three beads of the BB [9]. The latter will be referred to as MS3. Typical moves of SMS and MS3 are shown in Fig. 2. The SMS contains the single moves and the crankshaft motion. In addition to these moves, MS3 contains two and three-monomer moves. *The MS3 is shown to be more efficient than SMS* due to its great flexibility. Second, we study *the effect of SCs on the scaling of t_f* using cubic lattice Go models. At $T = T_{min}$ we have found $\lambda \approx 3.7$ which is higher than that for Go models without SCs. In other words, the scaling of folding times with N for chains with and without SCs is dramatically different.

The energy of a conformation with SC can be written as [7]

$$H = \epsilon_{bb} \sum_{i=1, j>i+1}^N \delta_{r_{ij}^{bb}, a} + \epsilon_{bs} \sum_{i=1, j \neq i}^N \delta_{r_{ij}^{bs}, a} + \epsilon_{ss} \sum_{i=1, j>i}^N \delta_{r_{ij}^{ss}, a}, \quad (2)$$

where ϵ_{bb} , ϵ_{bs} and ϵ_{ss} are BB-BB, BB-SC and SC

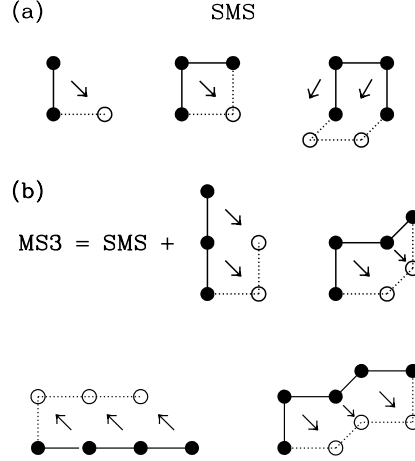


Fig. 2. (a) The single monomer and the crankshaft moves in the SMS. (b) Typical moves in the MS3. It includes all of the moves of the SMS and the two- and three-bead moves. The open circles denote new positions.

- SC interaction energies. The quantities r_{ij}^{bb} , r_{ij}^{bs} and r_{ij}^{ss} are the spatial distance between the i^{th} and j^{th} residues of the BB-BB, BB-SC and SC - SC, respectively. Self-avoidance, i.e. any BB and SC beads cannot occupy the same lattice site more than once, is imposed.

To study the effect of SCs we will consider Go models [6] in which ϵ_{bb} , ϵ_{bs} and ϵ_{ss} are chosen to be -1 for native contacts and 0 for non-native ones. Despite this simplification, as speculated by Tanaka [10], the Go models capture certain generic properties of protein folding. This is due to the fact that the geometry of the native state, and not details of interaction between amino acids, seems to play an important role in determining folding pathways and rates [11].

The rules for Monte Carlo backbone moves used in our kinetic study are as follows. In the SMS the possible moves are tail flip (20%), corner flip (20%) and crankshaft (60%) [12]. For MS3 we first enumerate all possible non-overlapping conformations of linear chains up to a maximum of $r_m + 2$ residues, where $r_m (= 3)$ is the maximum number of residues allowed to move in a single Monte Carlo step. The number of r residues to move is selected with an exponentially decaying probability [9]

$$P_r = \frac{(\gamma - 1)\gamma^{r_m}}{(\gamma^{r_m} - 1)\gamma^r}, \quad (3)$$

where $r = 1, \dots, r_m$, γ is set to be 1.35 which is an optimal value for folding. Once a segment of r residues is randomly chosen, one of the b_r neighboring conformations is selected with uniform probability as a new local conformation. Since b_r depends on the initial conformation of the segment, the move is accepted with probability b_r/b_r^{max} in order to satisfy the detail balance condition. b_r and b_r^{max} depend on whether the segment is bounded on one or both sides. If new positions for BB beads are allowed, then SC moves are determined. The Metropolis criteria is applied once the moves of both BB and SC beads are allowed geometrically. If an attempt involving a move of BB monomers fails then one tries to move the corresponding SC beads simultaneously [9].

We study the dependence of t_f and t_f^{bb} , the backbone folding time, on N . t_f is defined as the median of MC times to reach all (BB-BB, BB-SC and SC-SC) native contacts, whereas t_f^{bb} is the median of first passage times for BB-BB native contacts.

Fig. 3 shows the temperature dependence of the folding times obtained by the MS3 for the sequence whose native conformation is shown in Fig. 1. Clearly, the U-shape also holds for folding times of the BB. For the sequence studied T_{min} is the same for t_f and t_f^{bb} but it may not be valid for other sequences. The bottom of the U-shape curve is rather wide and this is a specific feature of Go and other optimized sequences. At low and high temperatures the native backbone contacts form before the whole chain folds. In this paper we focus on the scaling of folding times at $T = T_{min} \approx T_F$.

Fig. 4 shows the dependence of folding times obtained by two types of dynamics. To calculate the folding times we computed the distribution of first passage times from one hundred individual trajectories. The number of targets we used for $N = 9, 15, 18, 24, 28, 32$ and 40 are 100, 50, 50, 20, 17, 15 and 15, respectively.

We obtain $\lambda = 3.6 \pm 0.2$ and 3.7 ± 0.2 for MS3 and SMS, respectively. The power law behavior (1) is also valid for BB folding, i.e. $t_f^{bb} \sim N^{\lambda_{bb}}$. We found $\lambda_{bb} = 3.9 \pm 0.3$ and 3.9 ± 0.3 for MS3 and SMS, respectively. Within error bars $\lambda = \lambda_{bb}$ as

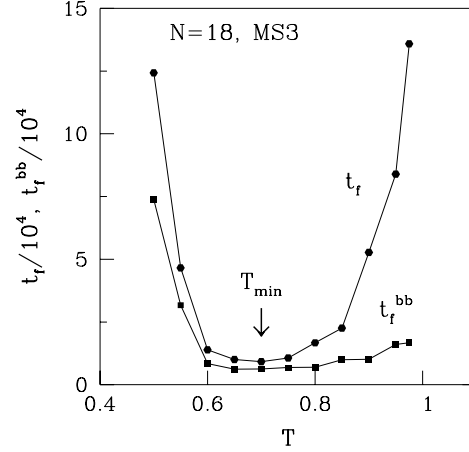


Fig. 3. The temperature dependence of t_f and t_f^{bb} using MS3 dynamics for the sequence shown in Fig. 1. The arrow indicates T_{min} .

expected. Interestingly, exponents λ and λ_{bb} obtained by two different move sets remain the same. Since exponent λ for Go models with SCs is higher than that for models without SCs [4,5] we conclude that they show different folding kinetics. Such differences apparently become much more enhanced for more realistic models of proteins [13]. Thus, it is reasonable to expect that dense side chain packing may provide additional folding barriers.

Although the scaling exponents are almost the same for two move sets, the dynamics have the visible effect on absolute values of folding times. This is demonstrated in the upper panel of Fig. 5 where the dependence of t_f^{SMS}/t_f^{MS3} on N is shown. The folding times obtained by the SMS are about two times longer than those by the MS3 but the real gain in CPU time is about one and half times due to the increased complexity of MS3. So, the MS3 proposed by Betancourt and Thirumalai is more efficient for folding lattice models, because MS3 involves more possible moves making dynamics more flexible.

The relation between time scales to fold the BB and the whole sequence is demonstrated in the lower panel in Fig. 5. The results for both move sets show that the BB native contacts of short chains can be reached relatively fast. As N increases the folding times t_f and t_f^{bb} become comparable.

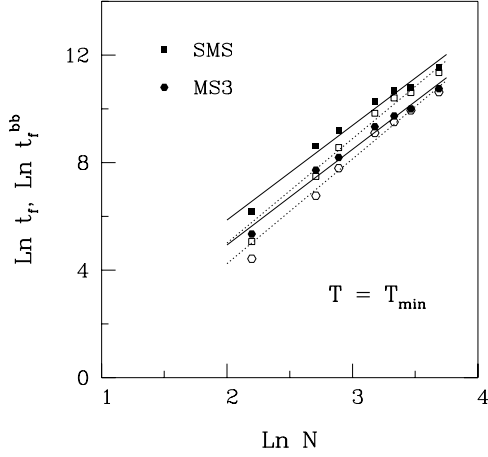


Fig. 4. Scaling of t_f and t_f^{bb} at $T = T_{min}$. The results were obtained by the SMS and MS3. The closed and open symbols denote t_f and t_f^{bb} . Straight solid and dotted lines are linear fits for t_f and t_f^{bb} , respectively. The results are averaged over 100, 50, 50, 20, 17, 15 and 15 target conformations for $N=9, 15, 18, 24, 28, 32$ and 40, respectively.

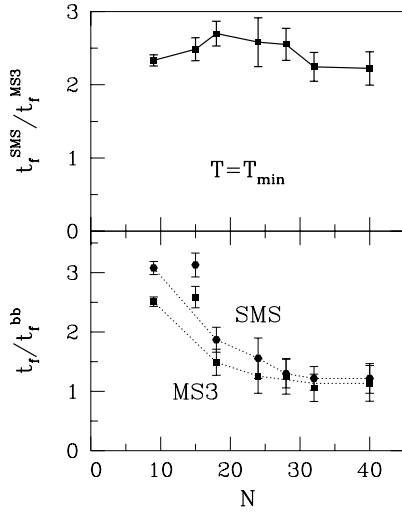


Fig. 5. The dependence of t_f^{SMS}/t_f^{MS3} on N (upper panel). The statistics are the same as in Fig. 4. The ratio t_f/t_f^{bb} obtained by the SMS and MS3 is shown in the lower panel. The results are obtained at $T = T_{min}$.

We now discuss the implication of our results for experiments. Recently, Plaxco *et al.* [14] suggested that for real proteins there is little correlation between the folding times and chain lengths. On the other hand, we have shown [13] that chain length

dependence must be incorporated to improve the correlation between folding rates and contact order [14]. Off-lattice protein models [15] also implicate a power law behavior (1) at T_{min} . Both experimental [14] and simulation [15] results are, however, based on one value of the chain length but not on large statistics. So the question about the scaling of t_f on N for real proteins remains open.

In conclusion, we have studied the scaling properties of Go sequences with SCs by two types of dynamics. The MS3 has proved to be a better choice for studying folding than the SMS. The models with and without SCs show different kinetic properties, such as distinct scalings with N .

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